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Temporal plus epilepsy is a major determinant of temporal lobe surgery failures

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Reasons for failed temporal lobe epilepsy surgery remain unclear. Temporal plus epilepsy, characterized by a primary temporal lobe epileptogenic zone extending to neighboured regions, might account for a yet unknown proportion of these failures. In this study all patients from two epilepsy surgery programmes who fulfilled the following criteria were included: (i) operated from an anterior temporal lobectomy or disconnection between January 1990 and December 2001; (ii) magnetic resonance imaging normal or showing signs of hippocampal sclerosis; and (iii) postoperative follow-up $\geqslant$ 24 months for seizure-free patients. Patients were classified as suffering from unilateral temporal lobe epilepsy, bitemporal epilepsy or temporal plus epilepsy based on available presurgical data. Kaplan-Meier survival analysis was used to calculate the probability of seizure freedom over time. Predictors of seizure recurrence were investigated using Cox proportional hazards model. Of 168 patients included, 108 (63.7%) underwent stereoelectroencephalography, 131 (78%) had hippocampal sclerosis, 149 suffered from unilateral temporal lobe epilepsy (88.7%), one from bitemporal epilepsy (0.6%) and 18 (10.7%) from temporal plus epilepsy. The probability of Engel class I outcome at 10 years of follow-up was 67.3% (95% CI: 63.4–71.2) for the entire cohort, 74.5% (95% CI: 70.6–78.4) for unilateral temporal lobe epilepsy, and 14.8% (95% CI: 5.9–23.7) for temporal plus epilepsy. Multivariate analyses demonstrated four predictors of seizure relapse: temporal plus epilepsy ($P < 0.001$), postoperative hippocampal remnant ($P = 0.001$), past history of traumatic or infectious brain insult ($P = 0.022$), and secondary generalized tonic-clonic seizures ($P = 0.023$). Risk of temporal lobe surgery failure was 5.06 (95% CI: 2.36–10.382) greater in patients with temporal plus epilepsy than in those with unilateral temporal lobe epilepsy. Temporal plus epilepsy represents a hitherto unrecognized prominent cause of temporal lobe surgery failures. In patients with temporal plus epilepsy, anterior temporal lobectomy appears very unlikely to control seizures and should not be advised. Whether larger resection of temporal plus epileptogenic zones offers greater chance of seizure freedom remains to be investigated.

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Abbreviations: ATL = anterior temporal lobectomy; SEEG = stereoelectroencephalography; SGTCS = generalized tonic-clonic seizures; TLE = temporal lobe epilepsy; TPE = temporal plus epilepsy

Introduction

The proportion of patients enjoying long-term postoperative seizure freedom following temporal lobe epilepsy (TLE) surgery remains suboptimal. Systematic reviews consistently report seizure freedom rate at short-term follow-up between 66–70% (Spencer and Huh, 2008; West *et al.*, 2015), with lower figures in randomized controlled trial (Wiebe *et al.*, 2001) and for longer term outcome (McIntosh *et al.*, 2001; Téllez-Zenteno *et al.*, 2005; de Asztely *et al.*, 2007; De Tisi *et al.*, 2011; Edelvik *et al.*, 2013; Ryvlin *et al.*, 2014). Furthermore, individual prediction of seizure relapse is hampered by the weak odds ratios associated with known predictors of TLE surgery failure (Tonini *et al.*, 2004; West *et al.*, 2015).

While recurrent seizures after surgery suggest that some epileptogenic tissue has not been resected, it is unclear whether this tissue is located within the operated temporal lobe (e.g. hippocampal remnant) (Wyler *et al.*, 1989; Awad *et al.*, 1991), the contralateral temporal lobe (Salanova *et al.*, 2005), or in ipsilateral extratemporal regions (Ryvlin and Kahane, 2005; Lopez-Gonzalez *et al.*, 2012; Elwan *et al.*, 2013). This latter situation can be further subdivided into pseudotemporal epilepsy whereby a strictly extratemporal epileptogenic zone was misdiagnosed (Elwan *et al.*, 2013), dual pathology combining an extratemporal epileptogenic lesion and hippocampal sclerosis (Li *et al.*, 1997, 1999; Lopez-Gonzalez *et al.*, 2012), and temporal plus epilepsy (TPE), defined as a primary temporal lobe epileptogenic zone extending to neighbouring regions, such as the insula, the suprasylvian operculum, the orbito-frontal cortex and the temporo-parieto-occipital junction (Ryvlin and Kahane, 2005; Barba *et al.*, 2007). TPE might be related to dual pathology but is most often encountered in patients with negative MRI or MRI signs of hippocampal sclerosis, thus posing a difficult diagnostic challenge in as much as it's clinical and scalp-EEG features only slightly differ from those encountered in TLE (Barba *et al.*, 2007).

To the best of our knowledge no study has yet investigated the role of TPE in accounting for TLE surgery failures. This was the primary objective of this multicentre study that focused on patients with MRI signs of hippocampal sclerosis or a normal MRI who underwent TLE surgery.

Subjects and methods

Study patients

Patients included in this study were selected from the epilepsy surgery cohorts launched in Grenoble and Lyon in 1990. Inclusion criteria were: (i) epilepsy surgery performed between January 1990 and December 2001, to maximize long-term postoperative follow-up; (ii) TLE surgery encompassing the anatomical boundaries of a standard anterior temporal lobectomy (ATL) as defined by Spencer *et al.* (1984): resection of the anterolateral 4.5 cm of the temporal lobe and of the medial temporal structures from the amygdala to the lateral ventricular atrium; (iii) MRI either normal or showing signs of hippocampal sclerosis; and (iv) postoperative follow-up $\geqslant$ 24 months for all patients classified as Engel outcome class I (Engel, 1993).

Presurgical evaluation

Presurgical evaluation was performed according to similar procedures in both centres during the census period, except for fluorodeoxyglucose (FDG)-PET, which was performed on a systematic basis only in Lyon, France. All patients underwent video-scalp EEG long-term monitoring and brain MRI. Non-invasive data were presented at local epilepsy conferences to provide a consensual conclusion regarding the most likely epileptogenic zone and decide to directly proceed to surgery or to perform an intracerebral stereoelectroencephalography (SEEG) procedure. Criteria to proceed directly to surgery were the following: (i) MRI signs of unilateral hippocampal sclerosis; (ii) interictal and ictal electroclinical findings judged typical for unilateral TLE; (iii) lack of initial ictal aphasia with preserved consciousness or very severe post-ictal aphasia that would suggest involvement of the posterior area of language within the epileptogenic zone; and (iv) lack of early ictal auditory illusion or hallucination that would suggest involvement of the posterior aspect of the superior temporal gyrus within the epileptogenic zone. Patients not fulfilling these criteria were offered a SEEG procedure.

While placement of SEEG electrodes is by definition individualized to the patient's electroclinical findings and anatomy, common rules applied to all patients from this series who underwent SEEG with the view to confirm a temporal lobe epileptogenic zone. Accordingly, the following regions were investigated in all patients on the side of suspected ictal onset: hippocampus, amygdala, anterior and posterior aspects of the superior, middle, and inferior temporal gyri, parahippocampal and fusiform gyri. From the mid-90s, the temporal

pole was also systematically implanted. Extra-temporal targets were selected based on the alternative hypotheses formulated regarding the location(s) and extent of the epileptogenic zone(s). The most frequently investigated brain regions were the temporo-parieto-occipital junction, fronto-basal and orbito-frontal cortex, suprasylvian operculum and insula, though almost all other cortical areas could be targeted. The insula was not implanted before 1995 and became routinely sampled thereafter. In patients where non-invasive data suggested the possibility of bitemporal epilepsy, electrodes were implanted in the hemisphere contralateral to that of the operated temporal lobe, mostly within its temporal lobe structures.

Surgical treatment

Similar to the decision to proceed or not to SEEG, the type and extent of surgical treatment was discussed and approved at local epilepsy conferences based on the review of available data.

In both centres, patients showing independent bitemporal seizures were not offered surgery with a single exception ($n = 1$) with unilateral hippocampal sclerosis, in whom interictal and ictal SEEG findings clearly predominated over the ipsilateral temporal lobe.

During the census period, patients from this series whose SEEG findings fulfil our current criteria for TPE (Ryvlin and Kahane, 2005; Barba *et al.*, 2007) were considered appropriate candidates for TLE surgery due to the primary involvement of the temporal lobe at seizure onset.

The great majority of surgical procedures were standard ATL. In a minority of patients, the anterior temporal lobe region was disconnected rather than resected, along the same anatomical boundaries as those of standard ATL.

Outcome assessment

Postoperative seizure outcome was assessed using the Engel postoperative outcome scale (Engel, 1993). The delay for seizures' recurrence corresponded to the delay between surgery and the first postoperative seizure. When seizures recurred between two follow-up appointments without detail on the exact date, the date of recurrence was taken as the midpoint of this time period.

For primary analysis, seizure-free patients were those achieving Engel outcome class I. In a sensitivity analysis, the seizure-free group was restricted to patients who were free from all seizures including aura (Engel class Ia).

Data reviewing

The clinical records of all included patients were reviewed to extract potential preoperative predictors of postoperative seizure outcome that are detailed further (Tonini *et al.*, 2004; West *et al.*, 2015).

In patients who underwent SEEG, the preoperative clinical reports detailing SEEG findings, and more specifically the site(s) of seizure onset, were used to define the extent of the epileptogenic zone, and conclude on the presence of unilateral TLE, bitemporal epilepsy or TPE according to the following criteria: (i) bitemporal epilepsy was defined as the occurrence of bilateral independent temporal lobe seizures; and (ii) TPE was defined as an epileptogenic zone including part of the temporal lobe and extending to neighbouring regions, such as the insula, the suprasylvian operculum, the orbito-frontal cortex and the temporo-parieto-occipital junction (Ryvlin and Kahane, 2005; Barba *et al.*, 2007). This conclusion was further confirmed by reviewing original SEEG traces. Patients who did not undergo SEEG were all considered to be suffering from TLE, understanding the potential for misclassification.

Preoperative scans were systematically reviewed to confirm accurate classification of MRI findings. Postoperative MRIs were also reviewed to evaluate the concordance between the operating plan and the tissue effectively resected. Hippocampal remnant was defined as the persistence of postoperative hippocampal tissue anterior to sylvius aqueduct according to the borders of standard anterior temporal lobectomy (Spencer *et al.*, 1984).

Statistical analysis

All relevant data were compared between patients with unilateral TLE and TPE using chi-square or Fisher's exact test and Student *t*-tests or Mann-Witney tests, where appropriate.

Kaplan-Meier survival analysis was used to calculate the probability of seizure freedom at various time points. Potential risk factors for seizure relapse were examined using Cox proportional hazards model. Specifically, association between Engel outcome class II–IV and the following factors was investigated: age at time of epilepsy surgery, epilepsy duration, study centre (Lyon, Grenoble), gender, febrile seizure during childhood, past history of traumatic or infectious brain insult, secondary generalized tonic-clonic seizures (SGTCS), MRI signs of hippocampal sclerosis, unilateral or bilateral interictal spikes on scalp-EEG, SEEG undertaken, type of epileptogenic zone (unilateral TLE or TPE, excluding the only patient with bitemporal epilepsy from analysis), surgical method (ATL or temporal disconnection), presence of postoperative hippocampal remnant.

Variables associated with $P < 0.1$ in univariate analyses were included in the multivariate Cox proportional hazards regression model. The level of significance of multivariate analyses was set at $P < 0.05$. All analyses were reprocessed to investigate association of the same risk factors and Engel outcomes other than class Ia. The same analyses were also performed within the subgroup of TLE patients to assess the role of the different risk factors once the major effect of a TPE epileptogenic zone was removed. All statistical analyses were performed using SPSS 13.0.

Results

The study comprised 78 males (46%) and 90 females (54%) whose clinical characteristics are detailed in Table 1. In brief, 131 of 168 patients (78%) demonstrated signs of hippocampal sclerosis including two where this abnormality was bilateral, and 108 patients (63.7%) underwent SEEG prior to TLE surgery. Among this latter group, one patient suffered from bitemporal epilepsy, and 18 fulfilled our criteria for TPE (10.7%) (Fig. 1). TPE epileptogenic zones included the fronto-basal cortex in two patients, the supra-sylvian operculum in four, the insula in seven

Table 1 Patients' characteristics

	All patients	TLE	TPE	*P*-value[a]
	168	150 (89.3)	18 (10.7)	
Study centre				ns
Grenoble	108 (64.3)	97 (65)	11 (61)	
Lyon	60 (35.7)	53 (35)	7 (39)	
Male gender	78 (46)	71 (47)	7 (39)	ns
Age at surgery				
Mean ± SD	31.7 ± 9.2	31.5 ± 8.8	32.8 ± 12.4	ns
Range	3–59	3–59	2.8–54	
Epilepsy duration				
Mean ± SD	22.4 ± 10.0	22.6 ± 9.8	20.5 ± 11.2	ns
Range	2.5–49	3.7–49	2.5–41	
Past medical history				
Febrile seizures in childhood	76 (45.2)	73 (49)	3 (17)	0.012
Traumatic or infectious brain insult	34 (20.2)	27 (18)	7 (39)	0.058
Secondary generalized seizures	70 (41.7)	59 (40)	11 (65)	0.068
Hippocampal sclerosis on MRI	131 (78.0)	122 (81)	9 (50)	0.005
Interictal scalp EEG findings				ns
No spike	30 (17.9)	26 (17)	4 (22)	
Unilateral temporal spikes	112 (66.7)	102 (68)	10 (56)	
Bitemporal spikes	26 (15.5)	22 (15)	4 (22)	
Intracranial EEG recordings	108 (63.7)	90 (60)	18 (100)	<0.001
Right-sided epileptogenic zone	94 (56.0)	87 (58)	7 (39)	ns
Type of surgery				
Anterior temporal lobectomy	151 (90)	135 (90)	16 (89)	ns
Temporal disconnection	17 (10)	15 (10)	2 (11)	
Postoperative hippocampal remnant	14 (8.3)	14 (100)	0	ns
Mean postoperative follow-up				
Mean ± SD	85.8 ± 36.7	85.4 ± 36.1	90.3 ± 39.2	ns
Range	6–120	6–120	14–-120	
Postoperative seizure outcome				<0.001
Engel Class I	118 (70.2)	115 (76.7)	3 (16.7)	
Engel class IA	97 (57.7)	94 (62.7)	3 (16.7)	
Engel class IB	8 (4.8)	8 (5.3)	0	
Engel class IC	2 (1.2)	2 (1.3)	0	
Engel class ID	11 (6.5)	11 (7.3)	0	
Patients free of AEDs	44 (26.2)	43 (28.7)	1 (5.5)	
Engel Class II–IV	50 (29.8)	35 (23.3)	15 (83.3)	
Engel class II	39 (23.2)	30 (20)	9 (50)	
Engel class III	4 (2.4)	1 (0.7)	3 (16.7)	
Engel class IV	7 (4.2)	4 (2.7)	3 (16.7)	

[a]Comparison between patients with TLE and those with TPE using chi-square or Fisher's exact test and Student *t*-tests or Mann-Whitney tests, where appropriate.
ns = not significant.

and the temporo-parieto-occipital junction in five. In comparison with TLE patients, patients with TPE had less frequent MRI signs of hippocampal sclerosis (50% versus 81%, $P = 0.005$) and past history of febrile seizures in childhood (17% versus 49%, $P = 0.012$), with a trend towards more frequent past history of traumatic of infectious brain insult (39% versus 18%, $P = 0.058$) and SGTCS (65% versus 40%, $P = 0.068$) (Table 1).

Surgery consisted of anterior temporal lobectomy in 151 patients (89.0%) and temporal disconnection in 17 (11.0%). These 17 disconnections were performed in 15 of 133 patients with TLE (11%), and in 2 of 18 patients with TPE (11%).

Postoperative MRI was available in 160 patients (95.2%) and showed hippocampal remnant on the side of TLE surgery in 14 patients with TLE (9.9%) and in none of the patients with TPE.

The mean postoperative follow-up was 85.8 ± 36.7 months (range 6–120 months) for the overall cohort, 83.5 ± 36.3 months (range 24–120 months) for patients achieving Engel outcome class I, and 91.8 ± 36.2 months (range 6–120) in those with Engel outcome class II–IV. This latter group included four patients (2.3%) with a follow-up <24 months.

Over the entire cohort, the probability of being seizure-free (Engel outcome class I) was 77.4% (95% CI: 74.2–

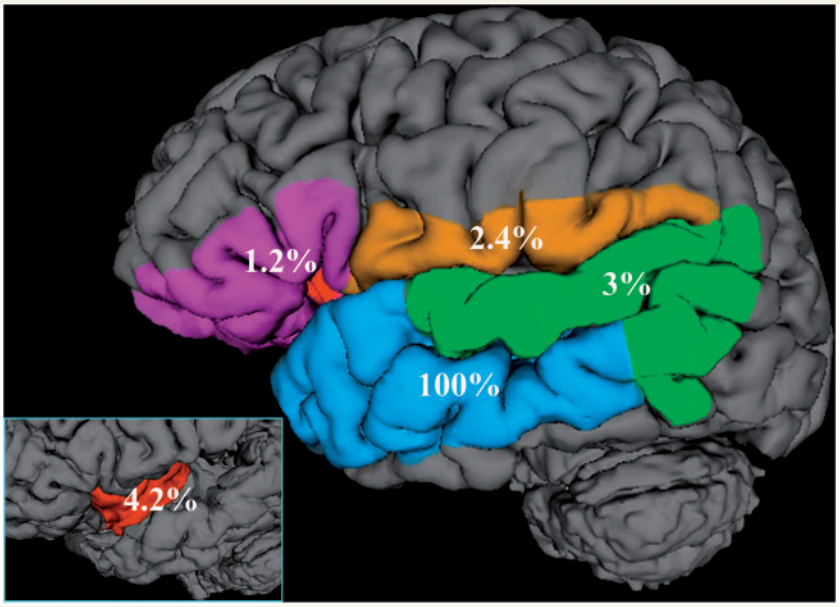

Figure 1 Percentage of patients in whom each particular delineated region is part of the epileptogenic zone. Due to the definition of TPE characterized by a primary temporal lobe epileptogenic zone extending to neighboured regions, in all patients the temporal lobe was included in the epileptogenic zone. Temporal lobe: blue; orbitofrontal cortex: violet; suprasylvian operculum: brown; insula: red; temporo-parieto-occipital junction lobe: green.

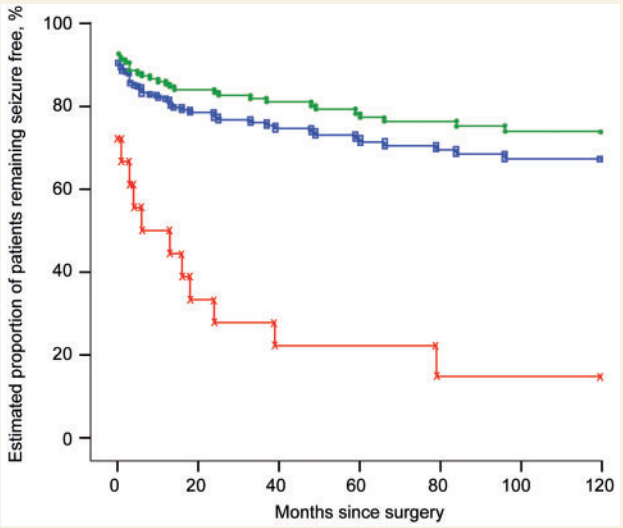

Figure 2 Long-term risk of seizure relapse following temporal lobe surgery. Kaplan-Meier analysis of time to seizure recurrence for all patients (blue/rectangles curve), patients with temporal lobe epilepsy (green/circles curve) and patients with TPE (red/cross symbols curve).

80.6) at 2 years of follow-up, 71.4% (95% CI: 67.8–75.0) at 5 years, and 67.3% (95% CI: 63.4–71.2) at 10 years (Fig. 2). The probability of being entirely seizure-free (Engel outcome class Ia) was 71.4% (95% CI: 67.9–74.9) at 2 years, 58.6% (95% CI: 52.6–62.6) at 5 years and 52.1% (95% CI: 47.7–56.5) at 10 years.

At last follow-up, 115 patients (77.2%) with unilateral TLE achieved Engel outcome class I, including 43 (28.9%) who were off treatment, whereas only three patients (16.7%) among the 18 with TPE were seizure-free, including one free of anti-epiletic drugs (5.6%) (Table 1). The only patient with bitemporal seizures who was offered surgery was in class II. The probability of seizure freedom 10 years after surgery was 74.5% (95% CI: 70.6–78.4) in patients with unilateral TLE and 14.8% (95% CI: 5.9–23.7) in those with TPE (Table 1 and Fig. 1). Among the 34 patients with unilateral TLE and Engel outcome class II–IV, 22 (65%) had undergone SEEG that failed to disclose TPE.

In univariate analyses (Table 2), Engel outcome class II–IV was associated with TPE ($P < 0.001$), past history of traumatic or infectious brain insult ($P = 0.014$), SGTCS ($P = 0.016$), and use of invasive recordings ($P = 0.043$). None of the other selected parameters were associated with seizure outcome.

In multivariate analyses (Table 2), Engel outcome class II–IV was associated with TPE ($P < 0.001$), postoperative hippocampal remnant ($P = 0.001$), past history of traumatic or infectious brain insult ($P = 0.022$), and SGTCS ($P = 0.023$). Risk of temporal lobe surgery failure was 5.06 (95% CI 2.36–10.82) greater in patients with TPE than in those with TLE.

When analyses were reprocessed for all Engel class outcome other than Ia, TPE remained the main predictor of seizure relapse in multivariate analysis ($P = 0.002$), while SGTCS and postoperative hippocampal remnant were no more significant (Supplementary Table 1).

In the TLE subgroup, multivariate analysis demonstrated two significant predictors of seizure relapse, i.e.

Table 2 Risk factors of seizure recurrence (Engel outcome class II–IV)

	Univariate analysis		Estimated % seizure free at 10 years (unadjusted) % (95% CI)	Multivariate analysis ($P < 0.001$)	
	HR (95% CI)	*P*-value		HR (95% CI)	*P*-value
All patients			67.3 (63.4–71.2)		
Study centre	1.07 (0.60–1.89)	0.82			
Age at surgery	0.99 (0.96–1.02)	0.541			
Epilepsy duration	0.99 (0.97–1.03)	0.931			
Gender	1.03 (0.59–1.79)	0.929			
Febrile seizures during childhood	0.72 (0.41–1.27)	0.257		–	–
Yes			72.9 (67.4–78.4)	–	–
No			62.9 (57.4–68.4)	–	–
History of traumatic or infectious brain insult	2.11 (1.16–3.82)	0.014		2.15 (1.12–4.15)	0.022
Yes			50.5 (41.3–59.7)		
No			71.9 (67.7–76.1)		
SGTCS	1.99 (1.14–3.48)	0.016		2.16 (1.11–4.18)	0.023
Yes			54.3 (47.5–61.1)		
No			76.3 (71.8–80.8)		
MRI signs of hippocampal sclerosis	0.59 (0.32–1.07)	0.082		0.94 (0.47–1.87)	0.863
Yes			70.5 (66.6–75.4)		
No			55.5 (46.5–64.5)		
Interictal spikes on scalp-EEG	–	0.166			
Unilateral temporal spikes	–	–			
No spike	0.69 (0.29–1.64)	0.397			
Bitemporal spikes	1.65 (0.85–3.21)	0.138			
Invasive EEG recording (SEEG)	1.96 (1.02–3.74)	0.043		1.46 (0.69–3.08)	0.320
Yes			62.4 (57.4–67.4)		
No			75.6 (69.1–82.1)		
Type of epilepsy	5.48 (3.13–10.84)	<0.001		5.06 (2.36–10.82)	<0.001
Unilateral TLE			74.5 (70.6–78.4)		
TPE			14.8 (5.9–23.7)		
Type of surgery	0.54 (0.17–1.75)	0.305			
Postoperative hippocampal remnant	2.11 (0.95–4.71)	0.068		4.62 (1.88–11.30)	0.001
Yes			50 (36.6–63.4)		
No			68.7 (64.2–72.9)		

HR = hazard ratio.

postoperative hippocampal remnant ($P = 0.002$) and SGTCS ($P = 0.016$) (Supplementary Table 2).

Discussion

Our study disclosed a previously unrecognized prominent preoperative predictor of surgical failure after ATL (West *et al.*, 2015), i.e. the presence of a temporal plus epileptogenic zone. This predictor was found to be associated with the highest hazard ratio (5.06; 95% CI: 2.36–10.82) in multivariate analysis incorporating classic predictors of post-ATL seizure outcome.

One needs to place this finding in the context of our current understanding of temporal lobe surgery failures and knowledge about TPE. Recurrent seizures after surgery suggest that some epileptogenic tissue has not been resected, either within (e.g. hippocampal remnant) (Awad *et al.*, 1991; Hennessy *et al.*, 2000) or outside the operated temporal lobe (ipsilateral extratemporal regions, contralateral temporal lobe) (Salanova *et al.*, 2005; Lopez-Gonzalez *et al.*, 2012; Elwan *et al.*, 2013), but the specific contribution of each of these various conditions to the overall rate of TLE surgery failure remains unknown (Tonini *et al.*, 2004).

TPE was proposed as a conceptual framework about a decade ago, based on the observation that some patients with TLE demonstrate an epileptogenic zone primarily involving the temporal lobe but extending to neighbouring regions, such as the perisylvian and orbito-frontal cortices and the temporo-parieto-occipital junction (Ryvlin and Kahane, 2005; Barba *et al.*, 2007). This observation was made possible by evolution in SEEG methodology during the 1990's, which enabled implantation of a greater number of electrodes and brain regions, including those listed above. Initial interpretation of these findings was not straightforward, however, and thought to be compatible with very fast propagation of TLE seizures that would

not necessarily affect postoperative outcome. Furthermore, extending TLE surgery to the perisylvian, frontobasal, or temporo-parieto-occipital regions carries significant risks, in particular on the side dominant for language, which prevented undertaking such resection at that time. Eventually, it was the recurrent observation of failed TLE surgery in patients with a larger than usual ictal onset zone that led to the TPE concept. In parallel, we observed that some ictal signs and clinical sequences allow us to suspect TPE (Barba *et al.*, 2007).

The strong association between TPE and risk of seizure relapse following ATL reported herein reinforces the view that TPE represents a distinct form of focal epilepsy that ought to be distinguished from TLE and should not be offered standard ATL. Additional validation would derive from the observation that larger resections, including the entire temporal plus epileptogenic zone, provide significantly better seizure outcome. The pattern of seizure relapse over time also appears to distinguish TPE from TLE. Indeed, while the latter showed immediate recurrence in ~10% of cases, followed by a steady and slowly progressive increase in surgical failures over the next 10 years, 87% of patients with TPE suffered seizure relapse within 2 years of surgery.

Three of the 18 patients with TPE (16.7%) were seizure-free following ATL. This finding might reflect the caveats of SEEG, whereby limited spatial sampling and qualitative interpretation can lead to erroneous conclusions or overestimation of the seizure onset zone. Alternatively, partial resection of the apparent epileptogenic zone might allow one to control seizures in some patients, as previously demonstrated in various situations where palliative temporal lobe surgery proved successful in 10–20% of cases (Wieser *et al.*, 1990; Fish *et al.*, 1991; Li *et al.*, 1997, 1999).

Conversely, 35 patients with a seemingly temporal epileptogenic zone suffered seizure recurrence following ATL. In one of them, independent bitemporal seizures were recorded and appear likely to account for surgical failure. Another seven patients demonstrated a hippocampal remnant on postoperative MRI, representing 14% of all surgical failures, and 21% of those with unilateral TLE. While reoperation of hippocampal remnant does not always lead to seizure freedom (Wyler *et al.*, 1989; Awad *et al.*, 1991; Schwartz and Spencer, 2001), the association between such a remnant and seizure outcome in both the entire cohort and the TLE subgroup, suggests that it directly contributes to surgical failures.

The remaining 27 patients, who failed ATL without evidence for TPE, bitemporal epilepsy, or hippocampal remnant, included 19 with and eight without SEEG investigation. While the latter might suffer TPE, this is less likely in the former, leaving a significant proportion of patients for whom the reason underlying ATL failure remains unknown.

Considering our entire series, i.e. TLE and TPE combined, the chance of achieving an Engel outcome class I was 67.3% at 10 years. This compares favourably with figures reported in other series where Engel outcome class I at 10 years of follow-up ranged from 41% to 70.8% (McIntosh *et al.*, 2001; Spencer and Huh, 2008; Elsharkawy *et al.*, 2009). Accordingly, one might speculate that these series also included a mixed population of TLE and TPE patients with the latter not being identified as a distinctive group.

Beside TPE and hippocampal remnants, two other weak predictors of poor seizure outcome were identified in our series, i.e. a past history of traumatic or infectious brain insult and the presence of SGTCS, in line with previous reports (McIntosh *et al.*, 2001; Jeha *et al.*, 2006; Uijl *et al.*, 2008; Elsharkawy *et al.*, 2009; West *et al.*, 2015). However, only the former remained significant in analyses contrasting Engel outcome class Ia with all other outcomes.

Several classic predictors of poor ATL outcome did not prove significant in our series, at least in multivariate analyses, including lack of febrile convulsions in childhood and of MRI signs of hippocampal sclerosis (West *et al.*, 2015), both of which were significantly more frequent in TPE than in TLE. Thus, their previously reported predictive value might have been primarily driven by their association to TPE, a stronger, albeit unrecognized predictor at that time. Furthermore, recent TLE series have failed to confirm an association between unilateral hippocampal sclerosis on MRI and surgical outcome (Bell *et al.*, 2009; LoPinto-Khoury *et al.*, 2012).

According to the paucity of independent and highly predictive biomarkers of temporal lobe surgery failure, it is currently challenging to develop a model that would allow invasive EEG investigations to be refused in patients whose non-invasive work-up remains compatible with either TLE or TPE. This was not the aim of this study, and we would advise deferring this issue until we know whether or not resections larger than ATL can provide an acceptable rate of seizure freedom in TPE.

Our study has several limitations. It remains retrospective by design as we reclassified patients as suffering from TPE based on *post hoc* review of SEEG reports, leading to a risk of bias in data analysis, as patient outcome was known; however, all relevant data used in this study were prospectively and systematically collected in both participating centres. Follow-up data during the past 2 years of census were not available in two-thirds of patients; however, the mean postoperative follow-up was 7 years with a minimum of 2 years in all those classified as Engel outcome class I. The subgroup of patients with TPE was relatively small but proved to represent a comparable proportion of the entire population selected in both Lyon (11.7%) and Grenoble (10.2%) centres. During the period covered by this study, preoperative 3 T MRI was not available, a weakness that might have resulted in an underestimation of the proportion of patients with MRI signs of mesial temporal sclerosis. The possibility of MRI-occult focal cortical dysplasia appears less likely as no such pathological finding was observed on the resected specimens. Finally, postoperative video-EEG data were not available in patients from this series who failed

TLE surgery. Such data might contribute to a better understanding of these surgical failures.

In conclusion, this series suggests that TPE represents a prominent cause of temporal lobe surgery failures in patients seemingly suffering from TLE with a normal MRI or MRI signs of hippocampal sclerosis. This finding supports the use of SEEG investigations with appropriately placed extra-temporal electrodes in patients whose past history or electroclinical data suggest the possibility of TPE. In patients with SEEG-confirmed TPE, ATL appears very unlikely to control seizures and should not be advised. Further studies are warranted to evaluate the efficacy of larger resections in TPE patients and to understand the cause of ATL failures in patients with a strictly unilateral temporal epileptogenic zone and lack of hippocampal remnant.

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Supplementary material

Supplementary material is available at *Brain* online.

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